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ART UNIT	**PAPER NUMBER**
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,158	BRASLAWSKY ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

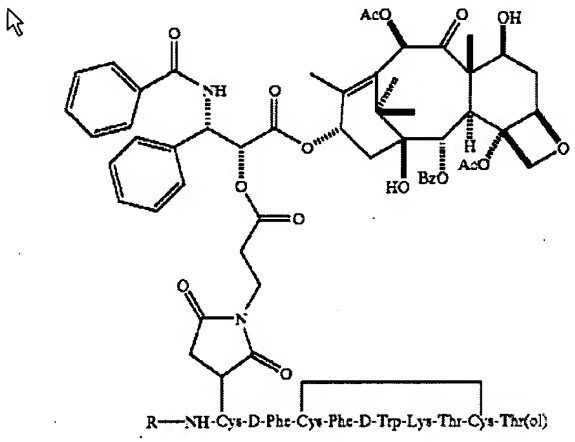
This Office Action is in response to the reply received on June 18, 2007.

Claims 15-20 are pending in the application. Claim 15 has been amended.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Applicants originally elected without traverse claims 15-20 (Group III), directed to methods of treating an SSTR-associated disorder. In response to the election of species requirement, Applicants elected the somatostatin analog wherein A is SEQ ID NO: 1 (claim 16) and B is SEQ ID NO:4 (claim 17), which is equivalent to the CP1 somatostatin analog of SEQ ID NO: 5 (claim 18).

The species was searched and found free of the prior art. The search was broaden to encompass claims SEQ IDs NOs: 1-7, which were found free of the prior art. The search was extended by Examiner to the species:



wherein A is cysteine or a peptide chain comprising one or more cysteine residues; R=H, wherein paclitaxel (a therapeutic agent) is bound to the cysteine residue via a thiol

linkage and B= octreotide (D-Phe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr(ol). The previous 103 rejection over this species has been overcome by Applicant's amendments to claim 15.

The search was broadened again and the method comprising administering to the subject a composition (e.g., column 14, lines 17-24) comprising a somatostatin analog of the formula (A-B) wherein A is a peptide chain comprising one or more cysteine residues (e.g., A is F007 as in Figure 6 and Example 10; column 13, lines 36-40; column 8, lines 10-45) and B is somatostatin (e.g., Example 10) as taught by Fukuta el al. (US 5,442,043) was rejected under 35 USC 102(b). Applicants have now amended the claims and have overcome this rejection.

The search has now been further broadened to encompassed the instantly amended claims 15-20. The species drawn to a method of treating an SSTR-associated disorder in a mammalian subject in need thereof comprising administering to the subject the conjugate comprising (a) a somatostatin analog of the formula A-B: cyclo(N-methyl)FYW$_D$KVHcyCH2COGGCK.amide conjugated to the therapeutic agent Tc-99m via a thiol linkage to the cysteine residue in A at an interior site was found.

Claims 15-20 are presented for examination on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the

conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence (e.g., "a therapeutic agent"), it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a

subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims ***are drawn to a method of treating an SSTR-associated disorder in a mammalian subject in need thereof comprising administering to the subject a conjugate comprising (a) a somatostatin analog of the formula (A-B) which comprises A, which is a peptide chain or a single amino acid comprising one or more cysteine residues and (ii) B, which is a naturally occurring or synthetic somatostatin peptide or fragment thereof, which binds to a somatostatin receptor and (b) a therapeutic agent, which is bound to the somatostatin analog (A–B) via a thiol linkage to the one or more cysteine residues of (A) at an interior site(s); whereby a SSTR-associated disorder is treated.*** In regards to the "somatostatin peptide or fragment thereof" term, this is a very broad generic definition, which is not adequately described and/or represented in the examples. Please note that the specification provides only one example, with a generic CP1 as somatostatin analog, for which the formula is not described, with a derivative of aurestatin E. By the same token, the peptides comprise the instant SEQ ID Nos: 1-7, however, no guidance is provided in terms of the sequence related to such larger peptides encompassing SEQ ID Nos: 1-7 to be used in the instant methods, nor does it provide teachings for how to find the variety of peptide derivatives, mutations, variants, analogs, fragments, peptoids, chemically modified peptides thereof as mentioned in the instant disclosure, page 9. In addition therapeutic agents (e.g., disclosure, pages 18-20) include any agents with activity against cancer or SSTR-related disease, therapeutic genes, immunostimulatory agents and so forth, therefore a mere statement that such compounds would be desirable for conjugation does not sufficiently provide ample written description pages describing the full breadth of the (A-B) thiol containing

conjugates for the biological activity of the instantly claimed method. The specification does provide examples of what qualify as compounds of the claimed invention (see, e.g, disclosure, Examples 1-5, pages 27-30), however, these are limited to a few examples such CP1-AEB, CP1-FKMMAE and CP1-MX-DTPA. Please note that pages 18-20 describe various desirable therapeutic agents but there is no conjugation therein with the instantly claimed compounds of formula (A-B) and only one example wherein the biological activity of the instantly claimed conjugates is tested. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 15 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations are very broad as the compound would comprise A-B and/or the many possible fragments thereof comprising this generic structure and elements. It must not be forgotten that the MPEP states that if a biomolecule, if described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims recite some functional and structural characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of conjugates with e.g., chemically modified peptides, peptoids, mutations, variants analogs, peptide derivatives, with therapeutic agents such as antiangiogenic agents, therapeutic genes, immunostimulatory agents, anticancer agents and so forth. The description requirement of the patent statute requires a

description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant's arguments

Applicant argues that the instant claims encompass a novel combination of known elements with known function to achieve a novel result. The instant specification teaches the skilled artisan how to select and combine the known elements, i.e., somatostatin peptides, fragments or variants thereof, and therapeutic agents, to derive the claimed conjugates that can be used to treat SSTR-associated disorders. Based upon the general teachings of how to combine these known elements and the specific examples provided in the originally filed application, the instant disclosure is sufficient to allow a skilled artisan to envision the genus of the A-B thiol-containing conjugates that are used in the methods as claimed.

Somatostatin peptides are well-known in the art are described in the specification on page 6, lines 11-21. Somatostatin peptides are peptides capable of binding to a somatostatin receptor (page 16, lines 11-12). Examples of such somatostatin peptides are included in the sequence listing (SEQ ID Nos. 4 and 8) and described in 16 patents

reference in the specification on page 6, lines 18-21, and specifically incorporated into the instant specification on pae 6, lines 18-21, and specifically incorporated into the instant specification by reference. Somatostatin peptides that are capable of binding to somatostatin receptors are well-characterized in the prior art. Thus, a skilled artisan understands amino acid residues and/or secondary or tertiary structures necessary for somatostain peptides to bind to somatostatin receptors. In addition, a skilled artisan is able to readily determine the binding ability of any particular somatostatin variant to a somatostatin receptor. Accordingly, the present application adequately describes the somatostatin peptides fragments and variants that are encompassed by the instant claims.

Therapeutic agents of the conjugates useful in the claimed methods are also adequately described. Therapeutic agents that may be used to make the instantly claimed compound combinations are disclosed, for example, on pages 17-20 in the specification as filed. These agents include radioisotopes, cytotoxins, immunostimulatory agents, anti-angiogenic agents, therapeutic genes and chemotherapeutic agents, which are further exemplified in the specification as filed (See, e.g., specific isotopes on page 18, lines 18-29; cytotoxins on page 18, lines 12-13; immunostimulatory agents on page 19, lines 14-20; anti-angiogenic agents on page 19, lines 21-31, to page 20, line 2). The instant specification also discloses that therapeutic agents, which are capable of forming a thiol linkage, are suitable for use in the present invention (e.g., page 4, lines 10-12). Thus, a skilled artisan can readily envision the genus of therapeutic agents that may be conjugated to the somatostatin analogs of the

present invention. In addition, the specification adequately describes how the A and B peptide chains may be combined to form somatostatin analogs and further combined with therapeutic agents to derive the instantly claimed conjugates. For example, the somatostatin analogs are designed so as to provide site-specific drug attachment via a thiol-linkage. The site for drug attachment is selected as an interior site removed from residues involved in ligand binding (see, page 7, lines 30-33 and page 8, lines 1-7). The tiol linkages are further described in the specification on pages 11-12 and include direct linkages, indirect linkages, such as with chelators, and stable and labile linkages. Thus, the specification provides a thorough description of the elements that may be used to derive the claimed A-B peptide thiol-containing conjugates as well as how these elements are combined.

In further support of the scope of the claims, the specification provides examples demonstrating the structures and biological activities of two species of somatostatin analog/therapeutic agent conjugates. Examples 4 and 5 describe the cytotoxic and anti-tumor effect of CP1-AEB and CP1-FKMMAE, respectively. As stated in Capon, the specification does not need to describe every permutation of a claimed combination to comply with the written description requirement. In the instant case, because the invention involves a novel combination of known elements having known biological activities (i.e., an ability of an A-B analog to bind a somatostatin receptor and an ability of a therapeutic agent to have a biological activity when delivered to a cell), the knowledge in the art is extensive. In addition, the level of skill in the art with respect to peptide engineering and conjugation is high. Thus, based upon the specific examples

provided in the specification, which are supported by the general teaching and knowledge in the art, as described above, a skilled artisan would understand the co-inventors to be in possession of the full scope of conjugates useful for performing the claimed methods.

In summary, similar to the facts in Capon, the instant specification teaches a skilled artisan how to select and combine components having known structure and function to derive the conjugates useful in the claimed methods. The specification further provides specific examples that demonstrate the structures and biological activities of the disclosed conjugates for their intended purpose, i.e., treating SSTR-associated disorders. Thus, the instant specification provides a skilled artisan with sufficient disclosure to allow him to readily envision the structure and properties of the conjugates for practice of the claimed methods.

Response to Arguments

Applicant's arguments have been carefully considered yet not deemed persuasive for the reasons set forth above and because the disclosure does not adequately described the instantly claimed somatostatin peptides, fragments and variants thereof, and the therapeutic agents to be conjugated therewith in the methods of treating all type of SSTR-associated diseases. The disclosure teaches that the term "somatostatin-associated", as used herein to describe a disease or disorder treatable by the disclosed peptide analogs, refers to a condition characterized by abnormal SSTR expression and/or function. This is a very generic definition which, although is further

explained as abnormal SSTR expression refers to somatostatin receptor expression on the surface of a specific normal cell type, which expression is at a level significantly greater than a surface expression level normally associated with that specific normal cell type, for example in tumors characterized as neuroblastomas and in acromegaly, or cancer referring to both primary and metastasized tumors and carcinomas of any tissue in a subject, including solid tumors arising from hematopoietic malignancies such as leukemias and lymphomas, neurocrine malignancies, as well as many other solid tumors such as breast, lung, renal, prancreatic, gastric, colon and brain (e.g., page 7, lines 3-15 and page 17, lines 9-23) which has not been adequately described in the disclosure and examples. In addition, the therapeutic methods instantly claimed encompass, e.g., gene therapy, such as administrating conjugates encompassing therapeutic genes (e.g., page 18, lines 10-17) linked to somatostatin peptides, derivatives, mutations, variants, analogs, fragments, peptoids, chemically modified peptides thereof (e.g., pages 7-11) which have also not been adequately described within the disclosure. The written description rejection is therefore maintained.

New grounds of rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Dean et al. (US 5,783,170) as evidenced by Nosco et al. (US 4,925,650).

A method for treating an SSTR-associated disorder in a mammalian subject in need thereof (e.g., column 11, lines 35-48), the method comprising administering to the subject a conjugate comprising (a) a somatostatin analog of the formula (A-B), which comprises (i) A, which is a peptide chain or a single amino acid comprising one or more cysteine residues and (ii) B, which is a naturally occurring or synthetic somatostatin peptide or fragment thereof, which binds to a somatostatin receptor (e.g., cyclo(N-methyl)FYW$_D$KVHcy(CH2COGGCK.amide; column 7, lines 1-55; column 9, line 54; column 12, lines 46-52; claims), and (b) a therapeutic agent, which is bound to the somatostatin analog (A-B) via a thiol linkage to one or more cysteine residues of (A) [A is CH_2COGGCK.amide] at an interior site(s) (e.g., which forms a thiol linkage to cysteine when using a therapeutic agent such as radiometal (e.g. Tc-99m), e.g., column 4, lines 1-41; column 6, lines 25-65; column 7, lines 20-31) and as evidenced by, e.g., Nosco et al. e.g., abstract); whereby a SSTR-associated disorder is treated (e.g., column 11, lines 35-48 and column 12, lines 14-26).

Therefore, the reference is deemed to anticipate the instant claims above.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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MMCG 10/07

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